REMARKS

Claims 1 and 4 – 15 remain active in the application. Undersigned counsel thanks Examiner Qazi for a brief telephone conversation about the current office acton, which is summarized below.

The present invention is direct to the treatment of cancer rather than graft-v-host disease (GVHD).

Claims 1 and 4 – 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al., Gastroenterology, July 1998, vol. 115, pp 28 – 35.

The Examiner asserts that the treatment disclosed in McDonald et al. was give to the same population using same compound, and would have inherently maintained the graft-v-leukemia (GVL) reaction, as claimed (OA page 5, lines 6 – 8). However, the patient populations are not the same. The patients studied in the McDonald reference had a specific degree of graft-v-host disease without regard to whether they had a cancer. And the study did not relate to mortality. It focused on measures of appetite, nausea, vomiting, abdominal pain, diarrhea, and stool frequency. Therefore, the McDonald results would not have suggesting that mortality in cancer patients could be significantly reduced by maintaining a certain level of graft-v-host reaction in the patient, in order to take advantage of the GVL effect.

As shown in the Brey Declaration submitted August 31, 2005, under 37 C.F.R. §1.132, the critical feature for reducing cancer mortality is to first perform allogeneic hematopoietic cell transplant therapy (a primary treatment of blood-borne cancers), then administer beclomethasone 17,21-dipropionate to control the symptoms of GVHD but still *maintaining* a graft-v-leukemia (GVL) reaction. This treatment eliminates or reduces the number of cancer cells in the blood and reduces the rate of cancer mortality.

McDonald does not suggest any reason to treat GVHD in a way that maintains some effects of the disease, nor does it suggest selecting cancer patients for this regimen. Accordingly, the present invention would not have been obvious within the meaning of 35 U.S.C. 103(a).

Claims 1 and 4 – 15 are rejected for obviousness-type double patenting over U.S. 6,096,731. However, the claims of the patent do not relate to treatment of cancer patients in particular, and its disclosure gives not hint that the mortality of cancer patients can be reduced by mainitinging a GVL reaction. Accordingly, the double patenting rejection should be withdrawn.

In summary, the claims are limited to the use of beclomethasone dipropionate given in at least two dosage forms to cancer patients as a way to reduce mortality from cancer. This effect has been shown in a clinical trial submitted to submitted to the U.S. Food and Drug Administration in support of a New Drug Application for orBec® ORAL BECLOMETHASONE DIPROPIONATE TABLETS. This study showed that patients treated with oral BDP, 2 mg four times daily for 50 days, have an improved outcome compared to patients treated with the same prednisone induction plus placebo, as measured by proportion of treatment failures at various time points, time to treatment failure to study day 80, as well as *survival* at transplant day 200. These improvements in outcome are achieved without an increase in clinically significant toxicity, yielding a favorable risk to benefit ratio. Nothing in the McDonald reference or the '731 patent would have made these results obvious to a person of ordinary skill in the art.

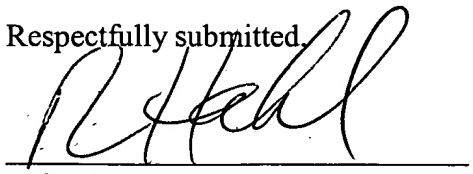
CONCLUSION

Applicants submit that the case is now in condition for allowance. Early notification of such action is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



Robert W. Hahl, PH.D.
Registration No. 33,893
Gilberto M. Villacorta, PH.D.
Registration No. 34,038

Date: November 7, 2005

KATTEN MUCHIN ROSENMAN, LLP
525 West Monroe Street
Chicago, Illinois 60661-3693
Facsimile: (312) 902-1061

GASTROENTEROLOGY 1998;115:28–35

Oral Beclomethasone Dipropionate for Treatment of Intestinal Graft-Versus-Host Disease: A Randomized, Controlled Trial

GEORGE B. McDONALD, MICHELLE BOUVIER, DAVID M. HOCKENBERY, JEAN M. STERN, TED GOOLEY, ALLEN FARRAND, CAROL MURAKAMI, and DOUGLAS S. LEVINE

Gastroenterology/Hepatology, Clinical Statistics, and Clinical Nutrition Sections, Division of Clinical Research, Fred Hutchinson Cancer Research Center and University of Washington School of Medicine, Seattle, Washington

See editorial on page 220.

Background & Aims: Beclomethasone dipropionate (BDP), a topically active steroid, seemed to be an effective treatment for intestinal graft-versus-host disease (GVHD) in a phase I study. The aim of this study was to compare the effectiveness of oral BDP to that of placebo capsules in treatment of intestinal GVHD. *Methods:* Sixty patients with anorexia and poor oral intake because of intestinal GVHD were randomized to receive prednisone (1 mg · kg^{-1} · day^{-1}) plus either oral BDP (8 mg/day) or placebo capsules. Initial responders who were eating at least 70% of caloric needs at evaluation on day 10 continued to take study capsules for an additional 20 days while the prednisone dose was rapidly tapered. The primary end point was the frequency of a durable treatment response at day 30 of treatment. *Results:* The initial treatment response at day 10 was 22 of 31 (71%) in the BDP/prednisone group vs. 16 of 29 (55%) for the placebo/prednisone group. The durable treatment response at day 30 was 22 of 31 (71%) vs. 12 of 29 (41%), respectively ($P = 0.02$). *Conclusions:* The combination of oral BDP capsules and prednisone was more effective than prednisone alone in treating intestinal GVHD. Oral BDP allowed prednisone doses to be rapidly tapered without recurrent intestinal symptoms.

Acute graft-versus-host disease (GVHD) affects the skin, liver, and intestine of patients who have received alloimmune T lymphocytes, usually in the setting of allogeneic marrow or stem cell transplantation.[1,2] Intestinal involvement with acute GVHD varies, from a moderate disease presenting with anorexia, vomiting, abdominal pain, and diarrhea to a fatal illness characterized by necrosis of the epithelium throughout the intestinal tract.[3–8] Treatment with high-dose corticosteroid therapy is usually effective but can be complicated by infections related to systemic immunosuppression and by side effects of corticosteroids.[2,9]

We recently reported the results of a phase I trial of a topically active corticosteroid, beclomethasone dipropionate (BDP), for the treatment of patients with intestinal GVHD.[10] In this trial, BDP capsules were given orally at 8 mg daily, half as enteric-coated capsules designed to dissolve in the alkaline pH of the upper small intestine and half as capsules that dissolve in the stomach. Significant improvement was found in appetite, oral intake, nausea, and diarrhea over the course of therapy with oral BDP alone and with oral BDP added to prednisone therapy. However, the time to improvement in patients receiving BDP as monotherapy was 7–14 days, which is longer than the response usually seen with prednisone therapy.

We have now completed a randomized, placebo-controlled, double-blinded trial of oral BDP plus 1 mg · kg^{-1} · day^{-1} prednisone vs. prednisone, 1 mg · kg^{-1} · day^{-1}, alone for treatment of patients with intestinal GVHD. Patients entering this trial had predominantly upper intestinal symptoms and little or no skin or liver GVHD, which would have required higher-dose immunosuppressive therapy.[2,9] A syndrome of upper intestinal involvement with GVHD was first described more than 10 years ago. Symptoms are largely those of nausea, vomiting, and persistent anorexia, sometimes accompanied by crampy abdominal pain and watery diarrhea.[3,4,11,12] The diagnosis is based on (1) endoscopic examination of the esophagus, stomach, and duodenum, which show a spectrum of abnormalities ranging from mucosal edema and patchy redness to ulceration and focal mucosal sloughing,[3,4,12–15] and (2) histological examination of mucosal biopsy specimens, which show apoptotic cells at the basal layer of esophageal epithelium and in the crypts of the stomach and duodenum.[12,13,15,16] In the

Abbreviations used in this paper: BDP, beclomethasone dipropionate; CI, confidence interval; CMV, cytomegalovirus; GVHD, graft-versus-host disease.

0016-5085/

present trial, we designed the treatment regimen to gain rapid control of symptoms by using prednisone for the first 10 days of treatment along with the study drug and to avoid systemic corticosteroid side effects by rapidly tapering the prednisone dose during 20 additional days of treatment with study drug. We felt that it was unethical to withhold prednisone treatment for patients with biopsy-proven acute GVHD. The primary objective of the study was to test the hypothesis that the durable response rate after 30 days of treatment was better in patients receiving prednisone plus oral BDP than in those receiving prednisone plus placebo capsules. A secondary objective was to examine the frequency of infection in the two groups.

Materials and Methods

Allogeneic Transplantation

Allogeneic marrow recipients received marrow-ablative chemotherapy and/or total body irradiation followed by donor hematopoietic cell infusion.[17-19] The source of hematopoietic cells was marrow in 47 patients and peripheral blood in 13 patients. Immunosuppressive drugs (listed in Table 1) were administered in the peritransplant period for prophylaxis against GVHD.[2,20]

Table 1. Patient Characteristics According to Treatment Group

	BDP + prednisone (n = 31)	Placebo + prednisone (n = 29)	*P* value
Age (yr) (±SD)	33.5 ± 11.8	38.8 ± 16.7	0.17
Gender			0.46
Female	20	16	
Male	11	13	
Diagnosis			
Chronic myeloid leukemia	10	11	
Acute myelogenous leukemia	9	5	
Myelodysplastic syndrome	2	7	
Acute lymphocytic leukemia	4	4	
Non-Hodgkin's lymphoma	3	2	
Aplastic anemia	2	0	
Paroxysmal nocturnal hemoglobinuria	1	0	
HLA status of hematopoietic cell donors			
Matched sibling	17	17	
Mismatched family member	4	2	
Matched unrelated donor	10	10	
Source of hematopoietic cells			0.21
Marrow	22	25	
Peripheral blood	9	4	
Drugs used for prophylaxis of acute GVHD			
Cyclosporine	2	1	
Methotrexate	1	0	
Cyclosporine + methotrexate	20	22	
Cyclosporine + prednisone	1	0	
Cyclosporine + trimetrexate	2	1	
Cyclosporine + methotrexate + daclizumab	2	0	
Tacrolimus + methotrexate	3	5	

Patient Selection

From August 1994 through January 1996, we enrolled 60 allogeneic hematopoietic cell recipients with biopsy-proven intestinal GVHD into a protocol approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. During this period, 374 patients had received allogeneic hematopoietic grafts, including 154 from HLA-matched unrelated donors. Grade II–IV acute GVHD developed in 163 patients.[2,8] Thus, the 60 patients enrolled represented 37% of patients with grade II acute GVHD. Diagnosis of acute intestinal GVHD required all of the following elements: (1) patients had to be at risk for GVHD because of engraftment from allogeneic hematopoietic cell donors; (2) upper intestinal endoscopy showed abnormal mucosa in the stomach and/or duodenum[3,4,12]; (3) histological findings in biopsy specimens of the gastric mucosa showed apoptotic crypt epithelial cells and crypt cell dropout, with or without focal lymphocyte infiltrates[6,7,12,13,16]; and (4) viral cultures of gastric biopsy specimens, histological stains of gastric biopsy specimens for bacteria and fungi (i.e., methenamine silver and Brown–Hopps tissue Gram's stains), histological evaluation for viral cytopathic effect, and the CLOtest for *Helicobacter pylori* (Delta West Pty. Ltd., Bentley, Western Australia) were negative.[14,21] We required that patients eat <70% of their estimated caloric requirements (the Basal Energy Expenditure multiplied by 1.3 for adults and by 1.4 for children <18 years old).[22] We also excluded patients with acute GVHD of the skin or liver that required systemic corticosteroid therapy, patients with any enteric or systemic infection, and patients requiring drugs that suppress gastric acid secretion.[23] Doses of drugs used to prevent acute GVHD were continued at the same doses as at study entry (Table 1).

Formulation of BDP and Placebo Capsules

Bulk crystalline beclomethasone 17,21-dipropionate was donated by the Schering-Plough Research Institute (Kenilworth, NJ). Both plain gelatin and enteric-coated gelatin capsules containing 1 mg BDP and lactose filler were prepared by the Division of Pharmaceutical Service, University of Iowa College of Pharmacy (Iowa City, IA), as described previously.[10,24] Patients received one uncoated and one enteric-coated capsule by mouth four times daily for a total daily dose of 8 mg. Placebo capsules prepared with and without enteric coating were dosed in the same way. Compliance was confirmed through capsule counts, examination of daily medication records, and weekly patient interviews.

Study Design

Consenting patients received either oral BDP capsules plus 1 mg · kg^{-1} · day^{-1} prednisone or placebo capsules plus 1 mg · kg^{-1} · day^{-1} prednisone according to a blocked random-

ization scheme with random-sized blocks. BDP or placebo capsules, identical in appearance, were distributed to patients by a pharmacist who received the results of randomization directly from a Clinical Statistics Section technician. Neither patients nor study personnel were aware of the contents of the study capsules. If patients could not tolerate oral prednisone, intravenous prednisolone at 80% of the calculated oral dose was used until oral prednisone could be tolerated. Randomization was stratified according to the amount of oral intake to have equal numbers of patients eating <40% of their caloric requirements treated on each arm. This was achieved by providing separate blocked randomization lists for each stratum. Patients were evaluated at the time of enrollment and after 10 days of treatment, using the scoring systems previously described for anorexia, nausea, vomiting, diarrhea, abdominal pain, intestinal bleeding, and Karnofsky performance score.[10] Daily caloric intake was calculated by a research dietitian from records of oral food and fluid consumption, as recorded by nutrition and nursing staff for hospitalized patients and by patients or family members for outpatients.

Patients whose treatment was successful after the initial 10 days continued to take study capsules while their prednisone dose was decreased, starting on day 11 of treatment and continuing through day 30 of treatment. The schedule of prednisone dose reduction was as follows: during days 11–13 of treatment, prednisone was given at 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$; during days 14–16 of treatment, at 0.25 $mg \cdot kg^{-1} \cdot day^{-1}$; and during days 17–30, at 0.125 $mg \cdot kg^{-1} \cdot day^{-1}$. Patients were reevaluated at day 20 and again at day 30 of treatment. At any time during the period from day 10 to day 30 of treatment, treatment could be judged to be a failure if the patient's caloric intake fell below 70% of requirements or if study medication was discontinued for any reason. Study capsules were discontinued in patients in whom treatment failed. All patients who were taking study capsules at the day 30 evaluation were followed up for an additional 10 days after abrupt discontinuation of both study capsules and prednisone.

Definitions: Success and Failure of Treatment

The primary end point of the study was the consumption of 70% or more of caloric needs after 30 days of treatment. As a secondary end point, we also determined whether patients were eating well after the first 10 days of treatment. Failure of treatment was defined as the inability to eat at least 70% of calculated caloric needs at the times of evaluation or as withdrawal from study because of medication intolerance, persistent symptoms, or appearance of acute GVHD in the skin or liver requiring treatment with higher-dose prednisone. If patients were withdrawn from study, their caloric intake and symptom scores on the day before withdrawal were recorded.

Infectious Complications

Patients who developed fever and signs of infection had the appropriate cultures and evaluations. All patients at risk for cytomegalovirus (CMV) infection had blood samples drawn at weekly intervals for determination of CMV antigenemia from day 10 after transplantation until discharge from Seattle.[25] As end points of infection, we recorded the days on which the body temperature reached 38.5°C; each episode of bacteremia, fungemia, and CMV antigenemia; and sinusitis, pneumonia, urinary tract infection, or any other episode of infection. Patients who developed diarrhea were evaluated for enteric bacterial pathogens, viruses, *Clostridium difficile*, and fungi, as described previously.[14]

Statistical Methods

The study was designed to detect a difference in true durable response rates of 80% in the group randomized to receive oral BDP to 40% in the group randomized to receive placebo, at a two-sided significance level of 0.05 with 90% power. Sample size calculations were performed using the normal approximation to the binomial distribution appropriate for comparing two proportions. Comparison of proportions were made using the χ^2 test, and comparisons of continuous variables and scores were made using the Mann–Whitney U test. No adjustments were made for multiple comparisons, and all reported P values are two sided. Analyses of response rates were done on an intent-to-treat basis.

Results

Patient Characteristics at Baseline

The patients in the two treatment groups were similar (Table 1). Recipients of HLA-mismatched or unrelated donor hematopoietic cells accounted for 14 of 31 patients in the BDP/prednisone group and 12 of 29 patients in the prednisone group. Most patients had profound anorexia and were eating, on average, <25% of their caloric requirements. There was a moderate amount of nausea, but signs of severe intestinal GVHD (refractory vomiting, profuse diarrhea, and abdominal pain) were infrequent (Table 2). The treatment groups were similar in their signs and symptoms of acute GVHD at enrollment (Table 2).

Initial and Durable Treatment Responses

Among 31 patients randomized to treatment with BDP capsules plus prednisone, 22 (71%; 95% confidence interval [CI], 52–86) were treatment successes after the initial 10 days of treatment (Table 3). Among 29 patients who received placebo capsules plus prednisone, 16 (55%; 95% CI, 36–74) were treatment successes after 10 days of treatment.

Only patients eating >70% of their caloric needs continued to take study drug, that is, 22 patients receiving BDP plus prednisone and 16 receiving placebo capsules plus prednisone. The prednisone dosage was

Table 2. Signs and Symptoms of Intestinal GVHD at the Time of Randomization According to Treatment Group

	BDP + prednisone (n = 31)	Placebo + prednisone (n = 29)	*P* value
No. of patients eating <40% of caloric requirements	24/31	21/29	0.77
Oral intake, as a % of estimated caloric requirements	21.5 ± 22.3	17.8 ± 20.9	0.50
No. of patients receiving total parenteral nutrition	25/31	27/29	0.27
Appetite score (0 = none, 5 = normal)	0.7 ± 1.1	0.7 ± 1.0	0.96
Nausea score (0 = none, 5 = severe)	1.7 ± 1.5	2.1 ± 1.6	0.37
Vomiting score (0 = none, 3 = extreme)	0.9 ± 1.1	0.8 ± 1.1	0.88
Abdominal pain score (0 = none, 5 = severe)	0.4 ± 0.8	0.5 ± 1.0	0.79
Diarrhea volume (*mL*)	161 ± 264	108 ± 147	0.34
Stool frequency (*no./day*)	1.7 ± 1.7	1.7 ± 1.4	0.98
Gastrointestinal bleeding score (0 = none, 4 = extreme)	0.1 ± 0.4	0.1 ± 0.4	0.94
Karnofsky performance score (0%–100%)	56.5 ± 10.5	55.2 ± 9.9	0.63

rapidly tapered in both groups. Over the ensuring 20 days, there were no treatment failures among 22 patients who were receiving oral BDP capsules as prednisone was being tapered, that is, all BDP-treated patients maintained appetite and caloric intake during this time. In contrast, 4 patients receiving placebo capsules plus tapering doses of prednisone were declared treatment failures because of recurrent intestinal symptoms and failure to eat (Figure 1). After 30 days of treatment, 17 of the original 29 patients receiving placebo capsules plus prednisone (59%; 95% CI, 39–76) were treatment failures. After 30 days of therapy, there were significantly more patients in the BDP group than in the placebo group who showed a durable response to treatment (71% vs. 41%; $P = 0.02$).

Signs and Symptoms of Intestinal GVHD After Treatment

One patient (UPN 9033), a 6-year-old girl, was able to swallow only 3 of 64 BDP capsules before being withdrawn from the protocol at day 8. She is considered a treatment failure at day 1 for the purposes of analysis, but as she ingested so few capsules, her individual symptoms were not considered evaluable. On the day of study drug discontinuation, patients randomized to receive BDP had significantly greater oral intake (97% ± 43% vs. 74% ± 35% of caloric needs; $P = 0.03$), better appetites (score, 3.9 ± 1.6 vs. 2.9 ± 1.6; $P = 0.02$), and less vomiting (score, 0.1 ± 0.4 vs. 0.4 ± 0.6; $P = 0.08$). Other symptoms (nausea, diarrhea, abdominal pain, performance score) had improved over baseline in both groups but were not statistically significantly different in BDP vs. placebo patients. Of 22 patients from the BDP group who were eating well at the day 30 evaluation, 6 developed poor appetites, intestinal symptoms, and inadequate intake over the next 10 days, whereas 16 (73%) remained well. Of 12 patients from the placebo group, 5 (42%) remained well ($P = 0.07$). These data suggest that among patients who achieved a durable response, those who had received BDP were more likely to maintain appetite after medications were discontinued.

Table 3. Response to Treatment After 10, 30, and 40 Days

	BDP + prednisone (n = 31)	Placebo + prednisone (n = 29)	*P* value
Initial successful response, day 10	22/31 (71%)	16/29 (55%)	0.2
Durable successful response, day 30	22/31 (71%)	12/29 (41%)	0.02
Posttreatment successful response, day 40	16/22 (73%)	5/12 (42%)	0.07

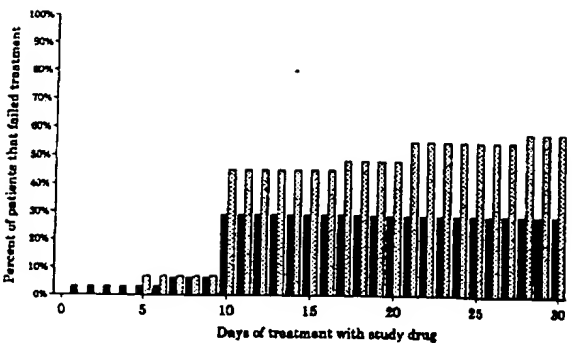


Figure 1. Time-to-treatment failure in patients randomized to oral BDP plus prednisone (■) vs. placebo plus prednisone (▨).

Acute and Chronic GVHD After Discontinuation of Study Medications

After discontinuation of study medications and completion of the observation period, we followed all patients to the current time or death, for development of acute and chronic GVHD.[2,8,26] After completion of the protocol, 5 of 60 patients developed grade III acute GVHD, 13 of 60 developed stage III skin GVHD, 2 of 60 stage III liver GVHD, and no patients developed stage III intestinal GVHD (Table 4). No patient developed grade IV acute GVHD. On long-term follow-up, 24 of 60 patients had developed clinical extensive chronic GVHD (Table 4). The frequency of acute and chronic GVHD was not different in the two treatment groups.

Table 4. Development of Acute and Chronic GVHD After Completion of Treatment With Either BDP Plus Prednisone or Prednisone Alone

	BDP + prednisone (n = 31)	Placebo + prednisone (n = 29)	P value
No. of patients with grade III acute GVHD	3/31 (10%)	2/29 (7%)	1.0
No. of patients with stage III acute GVHD of the skin	4/31 (10%)	9/29 (31%)	0.12
No. of patients with stage III acute GVHD of the liver	2/31 (6%)	0/29	0.49
No. of patients with stage III acute GVHD of the intestine	0	0	
No. of patients with clinical extensive chronic GVHD	11/31 (35%)	13/29 (45%)	0.60

Toxicity From Treatment

With the exception of the child who was unable to swallow capsules, the study capsules were well tolerated. We evaluated several parameters of infection to test the hypothesis that BDP treatment would lead to more intestinally derived and systemic infections than placebo treatment. There were no statistically significant differences in the two groups with regard to fever, bacteremia or fungemia, CMV antigenemia, or other infections (Table 5). The "other infections" category encompassed herpes viruses (herpes simplex virus, varicella-zoster virus, and CMV), respiratory viruses (influenza A, parainfluenza, respiratory syncytial virus), and urinary tract infections. Although the study was not powered to detect specified differences in these end points, the observed data offer no suggestion of meaningful differences. There were no enteric pathogens isolated and no deaths during the course of treatment in either group. The only death related to infection was in a patient assigned to treatment with placebo capsules plus prednisone who developed a disseminated fungal infection after discontinuation of study drug.

Discussion

This controlled trial shows that oral BDP is effective in treating the symptoms of intestinal GVHD, a lymphocyte-mediated form of inflammatory bowel disease. The combination of prednisone plus oral BDP achieved a greater frequency of initial responses after 10 days than prednisone alone. Oral BDP allowed prednisone to be rapidly tapered without a flare of intestinal symptoms in any patient, and the frequency of durable responses after 30 days of treatment was significantly higher than in patients receiving placebo capsules. Ethical considerations did not allow us to compare BDP as monotherapy to the standard therapy (prednisone, 1–2 $mg \cdot kg^{-1} \cdot day^{-1}$), but our phase I trial suggested that oral BDP was effective when given alone for treatment of upper intestinal GVHD.[10]

Our patient selection criteria excluded patients who require higher doses and longer duration of prednisone therapy, that is, patients with more severe, multisystem acute GVHD involving the skin, liver, and intestine.[2,9] High-dose immunosuppressive therapy in such patients would likely have obscured any immediate benefit from topical therapy with BDP. Nonetheless, because oral BDP has now been shown to be biologically active in treating intestinal GVHD, combination therapy might accelerate resolution of intestinal disease even in patients with severe multisystem GVHD. This approach has several potential advantages. Results of animal studies suggest

Table 5. Signs of Infection in Patients on Treatment

	BDP + prednisone (n = 30)	Placebo + prednisone (n = 29)	P value
Fever ≥38.5°C			
No. of days with fever ≥38.5°C	0.3 ± 0.9	0.3 ± 1.0	0.97
% of study days with fever ≥38.5°C	2 ± 9	3 ± 10	0.73
No. of patients with fever on study drug	4/30	4/29	1.0
Bacteremia or fungemia			
No. of episodes of bacteremia or fungemia	0.4 ± 1.2	0.3 ± 0.8	0.76
No. of episodes of bacteremia or fungemia per day on study drug	0.01 ± 0.04	0.03 ± 0.15	0.45
No. of patients with bacteremia or fungemia on study drug	5/30	4/29	1.0
CMV antigenemia			
No. of episodes of CMV antigenemia	0.4 ± 1.2	0.3 ± 0.7	0.53
% of study days on which there was CMV antigenemia	2 ± 5	1 ± 2	0.28
No. of patients with CMV antigenemia on study drug	7/30	5/29	0.75
Other episodes of infection			
No. of other episodes of infection (excluding bacteremia, fungemia, CMV antigenemia)	0.3 ± 0.6	0.4 ± 0.08	0.81
% of study days with other episodes of infections	1 ± 2	2 ± 5	0.18
No. of patients with other infections on study drug	8/30	8/29	1.0
Any infection			
No. of patients with any infection on study drug	15/30	14/29	1.0

that translocation of luminal organisms contributes to the morbidity of acute GVHD.[27,28] A more rapid restoration of intestinal mucosal integrity and resumption of enteral feeding could lessen translocation of luminal bacteria and endotoxin into the intestinal wall, lymphatics, and portal circulation.[29,30] In addition, any adjunctive therapy that would result in less systemic corticosteroid exposure would be useful because corticosteroid side effects and severe immunosuppression are important causes of morbidity and mortality in patients with acute GVHD. Not all patients who have biopsy-proven intestinal GVHD progress to severe, multisystem acute GVHD,[3,4] suggesting that dosing of immunosuppressive therapy can be more conservative than in patients who present with multisystem disease. For example, no patient in this series developed grade IV acute GVHD and few had grade III GVHD. Clinical extensive chronic GVHD, however, was frequent in both treatment groups (35% in patients receiving BDP plus prednisone and 45% in patients receiving prednisone alone). The frequency of chronic GVHD in the patients reported is nearly identical to that in our historical patients who received allogeneic marrow cells and whose acute GVHD had been treated with prednisone, 2 mg · kg^{-1} · day^{-1}.[26] Thus the use of potent topical corticosteroid therapy did not seem to lead to either severe acute GVHD of the skin or liver or to extensive chronic GVHD in the patient cohort that we studied.

Oral BDP seemed to be safe as judged by the infectious disease end points that we used. In our phase I trial, infections common to marrow transplant patients were noted,[10] but in this randomized trial the number and type of infections were similar in BDP and placebo groups. No enteric infections were seen, and the frequency of oropharyngeal infections was similar. Although the literature suggests that inhaled BDP may lead to pharyngeal and esophageal fungal infections,[31–33] we saw nothing similar in patients taking BDP as capsules.

We do not know the optimal dosing or formulation for topical therapy with BDP in this patient population. We studied a dose of BDP that had effected improvement in other patients with intestinal inflammation.[34–36] Upper intestinal symptoms of acute GVHD may respond better to a formulation that releases most of a given dose in the stomach. Ileal and colonic symptoms of GVHD may respond to capsules that are all enterically coated for release in the small intestine. The total daily dose of 8 mg may not be the maximally tolerated dose. However, in our phase I trial there was indirect evidence for absorption and circulation of a BDP metabolite, evinced by laboratory demonstration of suppression of the hypothalamic-pituitary-adrenal axis.[10] The clinical significance of this finding is unclear.[37] None of our phase I patients receiving BDP as monotherapy developed signs of hypercortisolism over 28 days, and none had signs of adrenal insufficiency. Nonetheless, the fact that there is some systemic exposure to BDP metabolites suggests that caution should be exercised in increasing the total daily dose.

We conclude that oral BDP is a useful adjunct to prednisone therapy in the treatment of intestinal GVHD and may prevent complications related to prolonged prednisone use. The avoidance of systemic immunosuppressive therapy may be particularly useful in patients who are at risk for serious fungal or viral infection.[38,39] The efficacy of BDP is probably achieved through the intraepithelial generation of beclomethasone monopropionate, a potent suppressor of T-cell function.[40] Although there is some systemic circulation of metabolites of orally delivered BDP, the drug probably acts topically within the intestinal mucosa because the amount of metabolite in the circulation is small, liver clearance is high, and clinical responses are independent of any systemic effect.[10,41,42] Oral BDP might also have a role as prophylaxis in recipients of HLA-mismatched and unrelated donor hematopoietic stem cells who are at high risk of acute intestinal GVHD.[43,44] Because the initial effector cells of acute GVHD in intestinal crypts are T lymphocytes in relatively small numbers,[1,45] BDP therapy may blunt the early cytokine release and apoptosis caused by T cells and thereby limit intestinal damage. Similarly, adding oral BDP to the initial therapy for acute GVHD may limit the extent of intestinal damage and, perhaps more importantly, may limit prolonged exposure to high-dose prednisone therapy.

References

1. Ferrara JLM, Cooke KR, Pan L, Krenger W. The immunopathophysiology of acute graft-versus-host disease. Stem Cells 1996;14: 473–489.
2. Sullivan KM. Graft-versus-host disease. In: Forman SJ, Blume KG, Thomas ED, eds. Hematopoietic cell transplantation. 2nd ed. Cambridge, MA: Blackwell Scientific, 1998 (in press).
3. Spencer GD, Hackman RC, McDonald GB, Amos DE, Cunningham BA, Meyers JD, Thomas ED. A prospective study of unexplained nausea and vomiting after marrow transplantation. Transplantation 1986;42:602–607.
4. Weisdorf DJ, Snover DC, Haake R, Miller WJ, McGlave PB, Blazer B, Ramsay NK, Kersey JH, Filipovich A. Acute upper gastrointestinal graft-versus-host disease: clinical significance and response to immunosuppressive therapy. Blood 1990;76:624–629.
5. Spencer GD, Shulman HM, Myerson D, Thomas ED, McDonald GB. Diffuse intestinal ulceration after marrow transplantation: a clinical-pathological study of 13 patients. Hum Pathol 1986;17: 621–633.

6. Snover DC. Graft-versus-host disease of the gastrointestinal tract. Am J Surg Pathol 1990;14(suppl 1):101–108.
7. McDonald GB, Sale GE. The human gastrointestinal tract after allogenic marrow transplantation. In: Sale GE, Shulman HM, eds. The pathology of bone marrow transplantation. New York: Masson, 1984:77–103.
8. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. 1994 Consensus conference on acute GVHD grading. Bone Marrow Transplant 1995;15:825–828.
9. Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, Beatty PG, Doney K, McDonald GB, Sanders JE, Sullivan KM, Storb R, Thomas ED, Witherspoon RP, Lomen P, Hannigan J, Hansen JA. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. Blood 1990;76:1464–1472.
10. Baehr PH, Levine DS, Bouvier ME, Hockenbery DM, Gooley TA, Stern JG, Martin PJ, McDonald GB. Oral beclomethasone dipropionate for treatment of human intestinal graft-versus-host disease. Transplantation 1995;60:1231–1238.
11. Wu D, Ponec RJ, Brentnall T, Joe RW, Kuver RP, Tzung S-P, Kim SU, Kim KA, Baehr PH, Shimoda NT, Malik R, Kraskouskas BJ, Todaro JL, Hockenbery DM, McDonald GB. Causes of nausea and anorexia in marrow transplant patients: a prospective study (abstr). Gastroenterology 1995;108:A945.
12. Roy J, Snover DC, Weisdorf S, Mulvahill A, Filipovich A, Weisdorf D. Simultaneous upper and lower endoscopic biopsy in the diagnosis of intestinal graft-versus-host disease. Transplantation 1991;51:642–646.
13. Washington K, Bentley RC, Green A, Olson J, Treem KR, Krigman HK. Gastric graft-versus-host disease: a blinded histologic study. Am J Surg Pathol 1997;21:1037–1046.
14. Cox GJ, Matsui SM, Lo RS, Hinds M, Bowden RA, Hackman RC, Meyer WG, Mori M, Tarr PI, Oshiro LS, Ludert JE, Meyers JD, McDonald GB. Etiology and outcome of diarrhea after marrow transplantation: a prospective study. Gastroenterology 1994;107:1398–1407.
15. Otero Lopez-Cubero S, Sale GE, McDonald GB. Acute graft-versus-host disease of the esophagus. Endoscopy 1997;29:S35–S36.
16. Snover DC, Weisdorf SA, Vercellotti GM, Rank B, Hutton S, McGlave P. A histopathologic study of gastric and small intestine graft-versus-host disease following allogeneic bone marrow transplantation. Hum Pathol 1985;16:387–392.
17. Forman SJ, Blume KG, and Thomas ED. Hematopoietic cell transplantation. Cambridge, MA: Blackwell Scientific, 1998 (in press).
18. Bensinger W, Buckner CD: Preparative regimens. In: Forman SJ, Blume KG, Thomas ED, eds. Hematopoietic cell transplantation. 2nd ed. Cambridge, MA: Blackwell Scientific, 1998 (in press).
19. Bensinger W, Appelbaum F, Rowley S, Storb R, Sanders J, Lilleby K, Gooley T, Demirer T, Schiffman K, Weaver C, Clift R, Chauncey T, Klarnet J, Montgomery P, Petersdorf S, Welden P, Witherspoon R, Buckner CD. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. J Clin Oncol 1995;13:2547–2555.
20. Storb R, Deeg HJ, Whitehead J, Appelbaum FR, Beatty P, Bensinger W, Buckner CD, Clift RA, Doney F, Farewell V. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft-versus-host disease after bone marrow transplantation for leukemia. N Engl J Med 1986;314:729–735.
21. Hackman RC, Wolford JL, Gleaves CA, Myerson D, Beauchamp MD, Meyers JD, McDonald GB. Recognition and rapid diagnosis of upper gastrointestinal cytomegalovirus infection in marrow transplant recipients: a comparison of seven virologic methods. Transplantation 1994;57:231–237.
22. Harris JA, Benedict FG. Biometric studies of basal metabolism in man. Washington, D.C.: Carnegie Institution of Washington, 1919; publication no. 279.
23. Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalization on bacterial colonization in critically ill patients. Crit Care Med 1989;17:211–216.
24. Levine DS, Raisys VA, Ainardi V. Coating of oral beclomethasone dipropionate capsules with cellulose acetate phthalate enhances delivery of topically active antiinflammatory drug to the terminal ileum. Gastroenterology 1987;92:1037–1044.
25. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogenec marrow transplantation: a randomized double-blind study. Blood 1996;88:4063–4071.
26. Sullivan KM, Agura E, Anasetti C, Appelbaum FR, Badger C, Bearman SI, Erickson K, Flowers M, Hansen J, Loughran T, Martin P, Matthews D, Petersdorf E, Radich J, Riddell S, Rovira D, Sanders J, Schuening F, Sladak M, Storb R, Witherspoon RP. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. Semin Hematol 1991;28:250–258.
27. Van Bekkum DW, Roodenburg J, Heidt PJ, van der Waaij D. Mitigation of secondary disease of allogeneic mouse radiation chimeras by modification of the intestinal microflora. J Natl Cancer Inst 1974;52:401–404.
28. Van Bekkum DW, Knaan S. Role of bacterial microflora in development of intestinal lesions from graft-versus-host reaction. J Natl Cancer Inst 1977;58:787–790.
29. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO. Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992;215:503–511.
30. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma: a prospective, randomized study. J Trauma 1986;26:874–881.
31. Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered dose inhaler alone and with Aerochamber. J Allergy Clin Immunol 1988;81:424–428.
32. Kesten S, Hyland RH, Pruzanski WR, Kortan PP. Esophageal candidasis associated with beclomethasone dipropionate aerosol therapy. Drug Intell Clin Pharm 1988;22:568–569.
33. Hemstreet MPB, Reynolds DW, Meadows J Jr. Esophagitis: a complication of inhaled sterold therapy. Clin Allergy 1980;10:733–738.
34. Elkon KB, Sher R, Seftel HC. Immunological studies of eosinophilic gastroenteritis and treatment with disodium cromoglycate and beclomethasone dipropionate. S Afr Med J 1977;52:838–841.
35. Levine DS. Immune modulating therapies for idiopathic inflammatory bowel disease. Adv Pharmacol 1994;25:171–234.
36. Rai RM, Hendrix TR, Moskaluk C, Levine DS, Pasricha PJ. Treatment of idiopathic lymphocytic enterocolitis with oral beclomethasone dipropionate. Am J Gastroenterol 1997;92:147–149.
37. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Am Rev Respir Dis 1993;148:S1–S26.
38. Bowden R. Fungal infection. In: Forman SJ, Blume KG, Thomas ED, eds. Hematopoietic cell transplantation. 2nd ed. Cambridge, MA: Blackwell Scientific, 1998 (in press).
39. Zaia J. Cytomegalovirus infection. In: Forman SJ, Blume KG, Thomas ED, eds. Hematopoietic cell transplantation. 2nd ed. Cambridge, MA: Blackwell Scientific, 1998 (in press).
40. Harris DM. Properties and therapeutic uses of some corticosteroids with enhanced topical potency. J Steroid Biochem Mol Biol 1975;6:711–716.
41. Martin LE, Tanner RJN, Clark TJH, Cochrane GM. Absorption and metabolism of orally administered beclomethasone dipropionate. Clin Pharmacol Ther 1974;15:267–275.

42. Oishi T, Deguchi T, Marumo H. Metabolic fate of beclomethasone 17,21-dipropionate in the rat. Pharmacometrics 1981;22:717–727.
43. Beatty PG, Hansen JA, Longton GM, Thomas ED, Sanders JE, Martin PJ, Bearman SI, Anasetti C, Petersdorf EW, Mickelson EM, Pepe MS, Appelbaum FR, Buckner CD, Clift R, Peterson FB, Stewart PS, Storb R, Sullivan KM, Tesler MC, Withersppon RP. Marrow transplantation from HLA-matched unrelated donors for treatment of hematologic malignancies. Transplantation 1991;51: 443–447.
44. Beatty PG, Anasetti C, Hansen JA, Longton GM, Sanders JE, Martin PJ, Mickelson EM, Choo SY, Petersdorf EW, Pepe MS, Appelbaum FR, Bearman SI, Buckner CD, Clift RA, Peterson FB, Singer J, Stewart PS, Storb RF, Sullivan KM, Tesler MC, Witherspoon RP, Thomas ED. Marrow transplantation from unrelated donors for treatment of hematologic malignancies: effect of mismatching for one HLA locus. Blood 1993;81:249–253.
45. Gallucci BB, Sale GE, McDonald GB, Epstein R, Shulman HM, Thomas ED. The fine structure of human rectal epithelium in acute graft-versus-host disease. Am J Surg Pathol 1982;6:293–305.

Received August 5, 1997. Accepted February 12, 1998.

Address requests for reprints to: George B. McDonald, M.D., Gastroenterology/Hepatology Section (D2-190), Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, P.O. Box 19024, Seattle, Washington 98109-1024.

Supported by grants from the U.S. Food and Drug Administration (FD-R-000827) and the National Institutes of Health (CA-18029 and CA-15704).

The authors thank Schering-Plough Research Institute, Kenilworth, NJ, for providing beclomethasone dipropionate.